PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* *AstraZeneca AB, Södertälje SE*
Applicant (s)

(21) *Patentansökningsnummer* *0202539-3*
Patent application number

(86) *Ingivningsdatum* *2002-08-27*
Date of filing

Stockholm, 2003-06-10

För Patent- och registreringsverket
For the Patent- and Registration Office

Hjördis Segerlund

Avgift
Fee *170:-*

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

COMPOUNDS

The present invention relates to compounds useful in the inhibition of metalloproteinases and in particular to pharmaceutical compositions comprising these, as well as their use.

The compounds of this invention are inhibitors of one or more metalloproteinase enzymes. Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases

or conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atherosclerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP-12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am J Pathol 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wildtype mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP-12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that smoking increases macrophage infiltration and macrophage-derived MMP-12 expression

in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000].

MMP13, or collagenase 3, was initially cloned from a cDNA library derived from a breast tumour [J. M. P. Freije *et al.* (1994) Journal of Biological Chemistry 269(24):16766-16773]. PCR-RNA analysis of RNAs from a wide range of tissues indicated that MMP13 expression was limited to breast carcinomas as it was not found in breast fibroadenomas, normal or resting mammary gland, placenta, liver, ovary, uterus, prostate or parotid gland or in breast cancer cell lines (T47-D, MCF-7 and ZR75-1). Subsequent to this observation MMP13 has been detected in transformed epidermal keratinocytes [N. Johansson *et al.*, (1997) Cell Growth Differ. 8(2):243-250], squamous cell carcinomas [N. Johansson *et al.*, (1997) Am. J. Pathol. 151(2):499-508] and epidermal tumours [K. Airola *et al.*, (1997) J. Invest. Dermatol. 109(2):225-231]. These results are suggestive that MMP13 is secreted by transformed epithelial cells and may be involved in the extracellular matrix degradation and cell-matrix interaction associated with metastasis especially as observed in invasive breast cancer lesions and in malignant epithelia growth in skin carcinogenesis.

Recent published data implies that MMP13 plays a role in the turnover of other connective tissues. For instance, consistent with MMP13's substrate specificity and preference for degrading type II collagen [P. G. Mitchell *et al.*, (1996) J. Clin. Invest. 97(3):761-768; V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550], MMP13 has been hypothesised to serve a role during primary ossification and skeletal remodelling [M. Stahle-Backdahl *et al.*, (1997) Lab. Invest. 76(5):717-728; N. Johansson *et al.*, (1997) Dev. Dyn. 208(3):387-397], in destructive joint diseases such as rheumatoid and osteo-arthritis [D. Wernicke *et al.*, (1996) J. Rheumatol. 23:590-595; P. G. Mitchell *et al.*, (1996) J. Clin. Invest. 97(3):761-768; O. Lindy *et al.*, (1997) Arthritis Rheum 40(8):1391-1399]; and during the aseptic loosening of hip replacements [S. Imai *et al.*, (1998) J. Bone Joint Surg. Br. 80(4):701-710]. MMP13 has also been implicated in chronic adult periodontitis as it has been localised to the epithelium of chronically inflamed mucosa human gingival tissue [V. J. Uitto *et al.*, (1998) Am. J. Pathol

152(6):1489-1499] and in remodelling of the collagenous matrix in chronic wounds [M. Vaalamo *et al.*, (1997) J. Invest. Dermatol. 109(1):96-101].

MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purified, then cloned and sequenced, in 1989 [S.M. Wilhelm *et al* (1989) J. Biol Chem. 264 (29): 17213-17221; published erratum in J. Biol Chem. (1990) 265 (36): 22570]. A recent review of MMP9 provides an excellent source for detailed information and references on this protease: T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases. 1998. Edited by W.C. Parks & R.P. Mecham. pp115 - 148. Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, it's expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive Pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic

implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues.

MMP-9 release, measured using enzyme immunoassay, was significantly enhanced in fluids and in AM supernantants from untreated asthmatics compared with those from other populations [Am. J. Resp. Cell & Mol. Biol., Nov 1997, 17 (5):583-591]. Also, increased MMP9 expression has been observed in certain other pathological conditions, thereby implicating MMP9 in disease processes such as COPD, arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

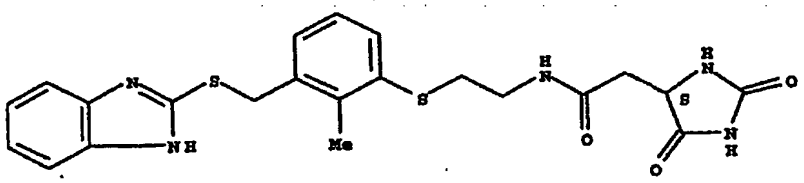
MMP-8 (collagenase-2, neutrophil collagenase) is a 53 kD enzyme of the matrix metalloproteinase family that is preferentially expressed in neutrophils. Later studies indicate MMP-8 is expressed also in other cells, such as osteoarthritic chondrocytes [Shlopov *et al*, 1997, Arthritis Rheum, 40:2065]. MMPs produced by neutrophils can cause tissue remodelling, and hence blocking MMP-8 should have a positive effect in fibrotic diseases of for instance the lung, and in degradative diseases like pulmonary emphysema. MMP-8 was also found to be up-regulated in osteoarthritis, indicating that blocking MMP-8 many also be beneficial in this disease.

MMP-3 (stromelysin-1) is a 53 kD enzyme of the matrix metalloproteinase enzyme family. MMP-3 activity has been demonstrated in fibroblasts isolated from inflamed gingiva [Uitto V. J. *et al*, 1981, J. Periodontal Res., 16:417-424], and enzyme levels have been correlated to the severity of gum disease [Overall C. M. *et al*, 1987, J. Periodontal Res., 22:81-88]. MMP-3 is also produced by basal keratinocytes in a variety of chronic ulcers [Saarialho-Kere U. K. *et al*, 1994, J. Clin. Invest., 94:79-88]. MMP-3 mRNA and protein were detected in basal keratinocytes adjacent to but distal from the wound edge in what probably represents the sites of proliferating epidermis. MMP-3 may thus prevent the epidermis from healing. Several investigators have demonstrated consistent elevation of MMP-3 in synovial fluids from rheumatoid and osteoarthritis patients as compared to controls [Walakovits L. A. *et al*, 1992, Arthritis Rheum., 35:35-42; Zafarullah M. *et al*, 1993, J. Rheumatol., 20:693-697]. These studies provided the basis for the belief that an

inhibitor of MMP-3 will treat diseases involving disruption of extracellular matrix resulting in inflammation due to lymphocytic infiltration, or loss of structural integrity necessary for organ function.

A number of metalloproteinase inhibitors are known (see for example the reviews of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282, and by Whittaker M. *et al*, 1999, Chemical Reviews 99(9):2735-2776). Different classes of compounds may have different degrees of potency and selectivity for inhibiting various metalloproteinases.

The following compound, *N*-{2-[3-(1*H*-Benzoimidazol-2-ylsulfanylmethyl)-2-methyl-phenylsulfanyl]-ethyl}-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide, is disclosed in WO2001034573 as an agent for treating infection of the gastric mucosa by *Helicobacter pylori*:

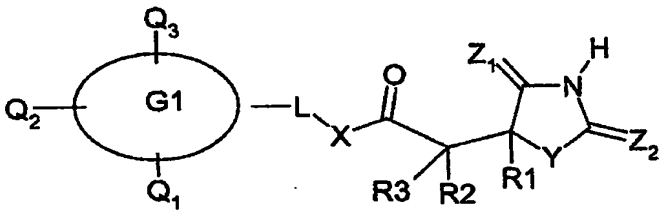


We have now discovered a new class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMPs such as MMP-12. The compounds are metalloproteinase inhibitors having a metal binding group that is not found in known metalloproteinase inhibitors. In particular, we have discovered compounds that are potent MMP12 inhibitors and have desirable activity profiles. The compounds of this invention have beneficial potency, selectivity and/or pharmacokinetic properties.

A metalloproteinase inhibitor compound is a compound that inhibits the activity of a metalloproteinase enzyme (for example, an MMP). By way of non-limiting example the

inhibitor compound may show IC50s *in vitro* in the range of 0.1-10000 nanomolar, preferably 0.1-1000 nanomolar.

In a first aspect of the invention we now provide compounds of the Formula 1



Formula 1

wherein

X is selected from NR4, O, CH2;

Y is selected from NH, N-methyl;

Z1 is selected from O, S, and **Z2** is selected from O, S, such that at least one of **Z1** and **Z2** is O;

R1 is selected from H, hydroxy, alkoxy, haloalkoxy, alkyl, heteroalkyl, heterocycloalkyl, aryl, heteroaryl, heterocycloalkylalkyl, alkylaryl, alkylheteroaryl, alkyl heterocycloalkyl, heteroalkylaryl, heteroalkylheteroaryl,arylalkyl, arylheteroalkyl,heteroarylalkyl, heteroarylheteroalkyl,arylaryl, arylheteroaryl,heteroarylaryl,heteroarylheteroaryl;

R1 is optionally substituted by one or more substituents selected from (C1-3)alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, thiol, alkylthiol, arylthiol, alkylsulfon, arylsulfon, aminosulfon, alkylaminosulfon, alkylaminosulfon, arylaminosulfon,primary, secondary or tertiary amino, amido, alkylamido, dialkylamido, cyano, sulfonamino, alkylsulfonamino, arylsulfonamino, amidino, N-aminosulfon-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitro-ethene-1,1-diamin, carboxylat, alkyl-carboxylat;

R2 is selected from H, (C1-3)alkyl;

R3 is selected from H, (C1-3)alkyl;

optionally R1 and R2 together with the carbon atoms to which they are attached may form a 5- or 6-membered saturated cycloalkyl or heterocyloalkyl ring;

optionally R2 and R3 together with the carbon atom to which they are attached may form a 5- or 6-membered saturated cycloalkyl or heterocyloalkyl ring;

R4 is selected from H, methyl, ethyl, isopropyl;

L is (C1-6)alkyl, (C1-6)alkynyl, or L is (C1-C5)heteroalkyl wherein the heteroalkyl contains a heteroatom or group selected from O, N, S, SO, SO2, CO, or L is selected from (C3-6)cycloalkyl, (C3-6)heterocycloalkyl;

L is optionally substituted with one or more substituents selected from (C1-4)alkyl, halogen, halo-(C1-4)alkyl, halo-(C1-4)alkoxy, (C1-4)alkoxy, wherein optionally a substituent may be attached to L at two points to form a ring or optionally a substituent may be attached to both L and G1 to form a ring;

G1 is a monocyclic, bicyclic or tricyclic group comprising one, two or three ring structures each of 3 to 7 ring atoms selected from cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, wherein at least one ring structure is aryl or heteroaryl;

when G1 is a bicyclic or tricyclic group each ring structure is joined to the next ring structure by a direct bond, by –O-, –S-, –NH-, –CO-, –CH2O-, -OCH2-, –CH2S-, -SCH2-, -C≡C-, -SO2-, -CH2, -NCO- or is fused to the next ring structure;

Q1, Q2 and Q3 are each independently selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

any alkyl radical within any of **Q1**, **Q2**, and **Q3** may itself be optionally substituted by one or more substituents selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

provided that the compound of Formula 1 is not *N*-{2-[3-(1*H*-Benzoimidazol-2-ylsulfanylmethyl)-2-methyl-phenylsulfanyl]-ethyl}-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide.

Unless otherwise stated:

any heteroalkyl group outlined above or below is a hetero atom-substituted alkyl containing one or more hetero groups independently selected from N, O, S, SO, SO2, (a hetero group being a hetero atom or group of atoms);

any heterocycloalkyl or heteroaryl group outlined above or below contains one or more hetero groups independently selected from N, O, S, SO, SO2;

any alkyl, alkenyl or alkynyl groups outlined above or below may be straight chain or branched; unless otherwise stated, any alkyl group outlined above or below is preferably (C1-7)alkyl and most preferably (C1-6)alkyl.

Preferred compounds of Formula 1 are those wherein any one or more of the following apply, most preferably all of the following apply:

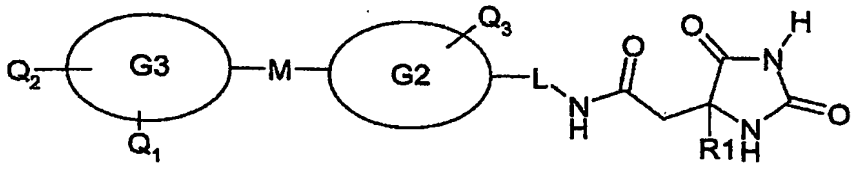
X is NH;

Y is NH;

Z1 and **Z2** are each O;

R2, R3 and **R4** are each hydrogen.

In a further aspect of the invention we now provide compounds of the Formula 2:



Formula 2

wherein

R1 is selected from H, (C1-6)alkyl, -(C1-6)alkylphenyl, -(C1-6)heteroalkyl, -(C1-6)alkyl-carboxylic acid, heterocycloalkyl, -(C1-6)alkyl-heterocycloalkyl, heteroaryl or -(C1-6)alkyl-heteroaryl; preferred heteroaryls are pyridine, diazines (such as pyrimidine) or azoles (such as imidazol), preferred heterocycloalkyls are morpholino, piperidine or piperazine; preferred heteroalkyls are amino-(C1-6)alkyl-; preferred substituents on heteroaryl are halogen, preferred substituents on amines in heteroalkyls and heterocycloalkyls are H, alkyl, alkylsulfon, alkylaminocarbonyl or alkyloxycarbonyl;

L is (C1-6)alkyl, (C1-6)alkynyl or **L** is (C1-5)heteroalkyl wherein the heteroalkyl contains a heteroatom or group selected from O, S, or **L** is (C3-6)cycloalkyl;

L is optionally substituted with one or more substituents selected from (C1-4)alkyl, halogen, halo-(C1-4)alkyl, halo-(C1-4)alkoxy, (C1-4)alkoxy, wherein optionally a substituent may be attached to L at two points to form a ring;

G2 is a 5- or 6-membered aryl or heteroaryl ring;

M is selected from a direct bond, -O-, -S-, -C≡C-, -CH2O-, -OCH2-;

G3 is a monocyclic or bicyclic group comprising one or two ring structures each of 3 to 7 ring atoms selected from cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, wherein when G3 is bicyclic at least one cyclic group is aryl or heteroaryl;

when G3 is a bicyclic group each ring structure is joined to the next ring structure by a direct bond, –O-, –S-, –NH-, –CO-, –CH2O-, –CH2S-, -C≡C-, -SO2-, -CH2, -NCO- or is fused to the next ring structure;

Q1, Q2 and Q3 are each independently selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

any alkyl radical within any of Q1, Q2, and Q3 may itself be optionally substituted by one or more substituents selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl.

For R1:

preferred heteroaryls are pyridine, diazines (such as pyrimidine) or azoles (such as imidazol);

preferred heterocycloalkyls are morpholino, piperidine or piperazine;

preferred heteroalkyls are amino-(C1-6)alkyl-;

preferred substituents on heteroaryl are halogen;

preferred substituents on amines in heteroalkyls and heterocycloalkyls are H, alkyl, alkylsulfon, alkylaminocarbonyl or alkyloxycarbonyl.

Preferred compounds of Formula 2 are those wherein any one or more of the following apply, preferably all of the following apply:

L is a ethyl chain optionally substituted with (C1-2)alkyl wherein the substituent may be attached to L at two points to form a ring, or L is (C3-6) cycloalkyl;

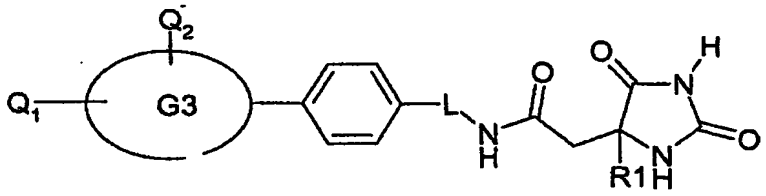
G2 is phenyl or G3 contains phenyl; most preferably G2 is phenyl;

Q3 is positioned at the ortho position to L when G2 is phenyl;

M is a direct bond;

when G3 is a bicyclic group each ring structure is joined to the next ring structure by a direct bond or is fused to the next ring structure.

In a further aspect of the invention, we provide compounds of the Formula 3:

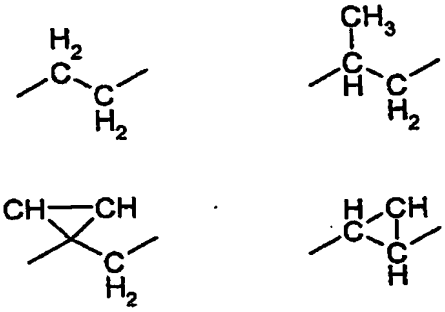


Formula 3

wherein

R1 is selected from H, (C1-6)alkyl, -(C1-6)alkylphenyl, -(C1-6)heteroalkyl, -(C1-6)alkyl-carboxylic acid, heterocycloalkyl, -(C1-6)alkyl-heterocycloalkyl, heteroaryl or -(C1-6)alkyl-heteroaryl;

L is selected from:



G3 is a monocyclic group or G3 is a fused bicyclic group comprising two ring structures each of 3 to 7 ring atoms selected from aryl or heteroaryl;

Q1 and Q2 are each independently selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

or Q1 is a group W-U-V-

wherein

V is attached to G3 and V is selected from CH2, O, S, SO, SO2, N, NCO, CON, OCON, NCON, NSO2, SO2N or CO;

U is (C1-C5)alkyl;

W is selected from hydroxy, amino, (C1-3)alkylamino, (C1-3)alkylamido, (C1-3)alkylcarbamate, (C1-3)alkylurea, cyano or (C1-3)alkyl sulfonyl;

optionally W may be attached to G3 so that together W, U, V and G3 from a ring.

For **R1**:

preferred heteroaryls are pyridine, diazines (such as pyrimidine) or azoles (such as imidazol);

preferred heterocycloalkyls are morpholino, piperidine or piperazine;

preferred heteroalkyls are amino-(C1-6)alkyl-;

preferred substituents on heteroaryl are halogen;

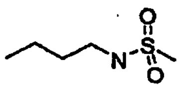
preferred substituents on amines in heteroalkyls and heterocycloalkyls are H, alkyl, alkylsulfon, alkylaminocarbonyl or alkyloxycarbonyl.

Most preferably **R1** is selected from H or methyl.

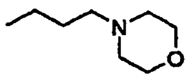
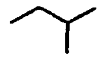
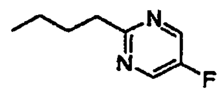
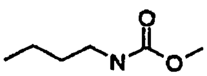
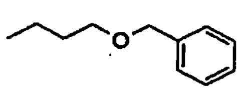
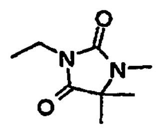
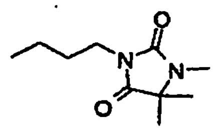
G3 is preferably selected from phenyl, pyridyl, thiophene, pyrrole, furane, oxazole, naphtalene, indole, bensofurane, bensothiophene, quinoline or isoquinoline.

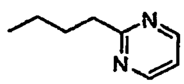
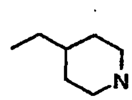
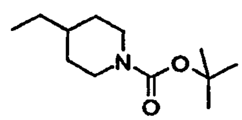
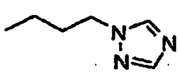
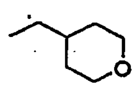
Q1 and **Q2** are preferably positioned at meta or para positions when **G3** is a 6-membered ring.

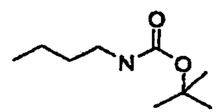
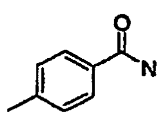
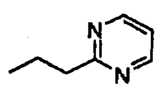
Suitable values for **R1** in compounds of Formula 1, 2 and 3 include the following:

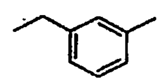


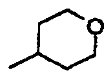
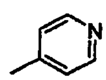
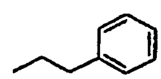
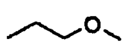
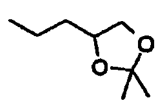
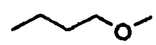
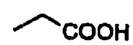
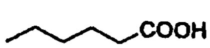
(propylaminosulfonylmethyl)

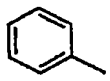






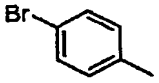




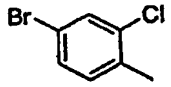


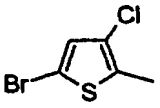










Suitable values for G1 or G3-M-G2 in compounds of formula 1 and 2 include the following:

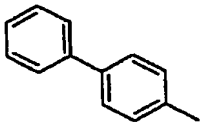


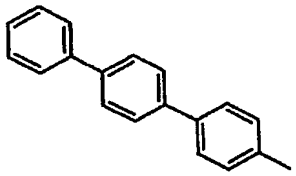


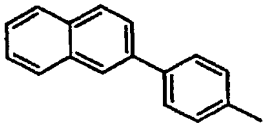


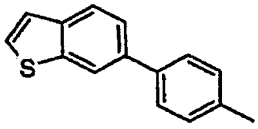


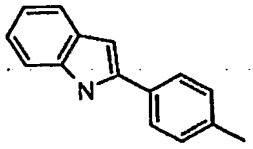
(phenyl)

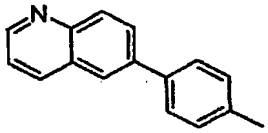


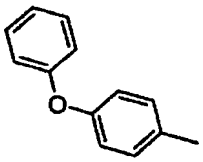


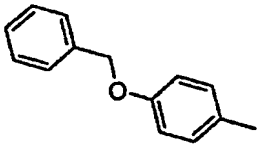


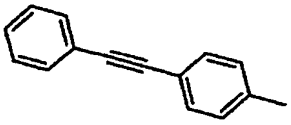


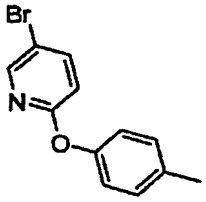


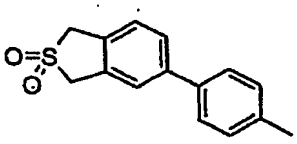












It will be appreciated that the particular substituents and number of substituents in compounds of the invention are selected so as to avoid sterically undesirable combinations.

Each exemplified compound represents a particular and independent aspect of the invention.

It will be appreciated that the compounds according to the invention may contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres (chiral centres) in compounds according to the invention can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof. Racemates may be separated into individual optically active forms using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, p104-107) including for example the formation of diastereomeric derivatives having convenient optically active auxiliary species followed by separation and then cleavage of the auxiliary species.

Where optically active centres exist in the compounds of the invention, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are inhibitors of MMP12. Each of the above indications for the compounds of the formulae 1, 2 or 3 represents an independent and particular embodiment of the invention.

Certain compounds of the invention are of particular use as inhibitors of MMP13 and/or MMP9 and/or MMP8 and/or MMP3.

Compounds of the invention show a favourable selectivity profile. Whilst we do not wish to be bound by theoretical considerations, the compounds of the invention are believed to show selective inhibition for any one of the above indications relative to any MMP1 inhibitory activity, by way of non-limiting example they may show 100-1000 fold selectivity over any MMP1 inhibitory activity.

The compounds of the invention may be provided as pharmaceutically acceptable salts. These include acid addition salts such as hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine.

They may also be provided as *in vivo* hydrolysable esters. These are pharmaceutically acceptable esters that hydrolyse in the human body to produce the parent compound. Such esters can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo* hydrolysable esters for carboxy include methoxymethyl and for hydroxy include formyl and acetyl, especially acetyl.

In order to use a metalloproteinase inhibitor compound of the invention (a compound of the formula 1, 2 or 3) or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention (a compound of the formula 1, 2, or 3) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester and pharmaceutically acceptable carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially)

with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.5 to 75 mg/kg body weight (and preferably of 0.5 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease or condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

Therefore in a further aspect, we provide a compound of the formula 1,2 or 3 or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof for use in a method of therapeutic treatment of the human or animal body or for use as a therapeutic agent. We disclose use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes. In particular we disclose use in the treatment of a disease or condition mediated by MMP12 and/or MMP13 and/or MMP9 and/or MMP8 and/or MMP3; especially use in the treatment of a disease or condition mediated by MMP12 or MMP9; most especially use in the treatment of a disease or condition mediated by MMP12.

In yet a further aspect we provide a method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a compound of the formula 1, 2 or 3 or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof. We also disclose the use of a compound of the formula 1, 2 or 3 or a pharmaceutically acceptable salt or *in vivo* hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes.

Metalloproteinase mediated diseases or conditions include asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases

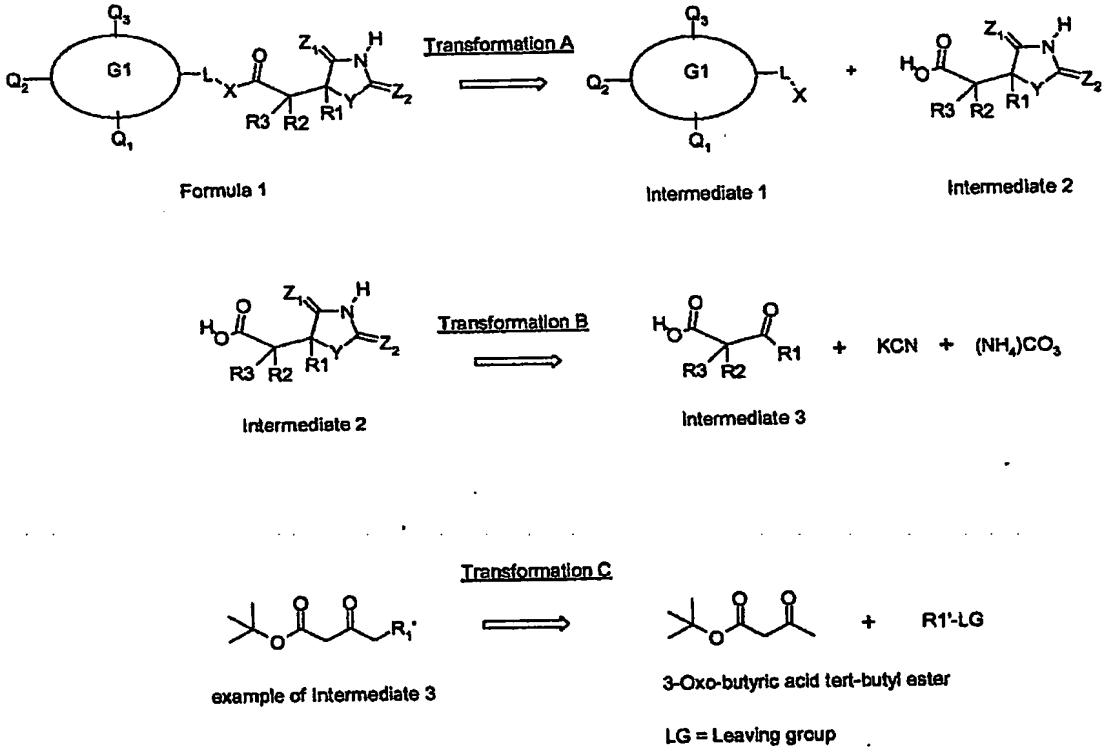
involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), hematological disorders.

Preparation of the compounds of the invention

In another aspect the present invention provides a process for preparing a compound of the Formula 1, 2 or 3 or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as described below. It will be appreciated that many of the relevant starting materials or intermediates are commercially or otherwise available or may be synthesised by known methods or may be found in the scientific literature. It will also be appreciated that a compound of the invention may be converted to a salt by known methods.

Scheme 1 shows three main retro synthetic transformations (A, B and C) that may be used to prepare compounds of Formula 1.

Scheme 1



Formula 1

Intermediate 1

Intermediate 2

Intermediate 2

Intermediate 3

example of intermediate 3

3-Oxo-butyric acid tert-butyl ester

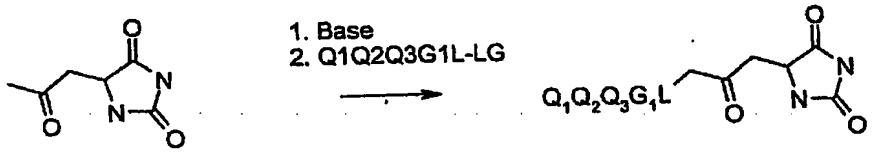
Transformation A

Synthesis of compounds where X is N or O requires a simple amide or ester coupling by an amine or alcohol of intermediate 1 to the carboxylic acid intermediate 2. The acid must be activated in some way, for example as the acid halide, anhydride, acyl urea or acyl derivative of N-hydroxysuccinimide. Preparation of amides and esters is described, for example, in Carey, F.A. and Sundberg, J., Advanced Organic Chemistry, 3 ed. pp 144-152, 1990.

For synthesis of ketones (where X = C), a suitable preparative method involves activating intermediate 2 by preparing the Weinreb amide in situ. This is followed by reaction of the amide with a suitable organometallic anion (as, for example, described in Tetrahedron letters 1999, 40 (16), 3123-3124).

Alternatively the dianion of a methyl-oxo-alkyl derivative such as 5-(2-oxo-propyl)-imidazolidine-2,4-dione may be alkylated by Q1Q2Q3G1L-LG in a method analogous to transformation C. LG is a leaving group (for example a halide or sulfonate), schematically depicted in Scheme 2. Suitable protecting groups are needed in this reaction, such as para-metoxy-benzyl or ter-butyl carbamate.

Scheme 2



Intermediate 1 is commercially or otherwise available or may be synthesised by known methods or may be found in the scientific literature. Example 1 herein describes the general synthesis of substituted 2-biphenyl-4-yl-ethylamines.

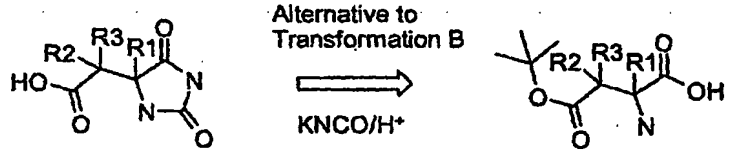
Transformation B

Transformation B is a dioxo-imidazolidin or oxo-thioxo-imidazolidin synthesis from the corresponding ketone or aldehyde (R1 = H). Preferably the carboxylic acid is protected, for example as the tert-butyl ester (se T.W. Greene and P.G. Wuts, Protective Groups in Organic Synthesis, second edition, Wiley, 1991 which discusses utilization of this protecting group). An oxo-thioxo-imidazolidin (Z_1 = S) may be prepared by reacting the ketone or aldehyde with thiocarbamic acid and sodium cyanide solved in ethanol and water

during suitable conditions (J. Chem. Soc 1959, 396). The dioxo-imidazolidin derivative is prepared in an analogous way by exchanging the thiocarbamic acid to ammonium dicarbonate (Henze; McKee; J.Amer.Chem.Soc.; 64; 1942; 1672.)

Other methods are available for preparing intermediate 2. For example, a wide range of α-amino acids are useful as synthons to dioxo-imidazolidin and oxo-thioxo-imidazolidins (see Scheme 3). It is well known that salts of cyanic acid, urea, or thiocyanic acid together with a ammonium salt, reacts with α-amino acids to form these heterocycles (Anteunis, M.J.O.; Spiessens, L.; Witte, M. De; Callens, R.; Reyniers, Bull.Soc.Chim.Belg.; EN; 96; 6; 1987; 459-466, Dakin; Am.Chem.J.; 44; 1910; 49 , Haurowitz et al. J.Biol.Chem.; 224; 1957).

Scheme 3



Example of Intermediate 2 alpha-amino acid

Several suitable dioxo-imidazolidin and oxo-thioxo-imidazolidin acids are commercially available or are described in the literature (for example, those shown in List 1 below).

List 1

Examples of suitable intemediate 2 (with CAS registry number in brackets)

(2,5-dioxo-imidazolidin-4-yl)-acetic acid *(5427-26-9, 26184-52-1, 26184-53-2, 67337-71-7);*

(3-methyl-2,5-dioxo-imidazolidin-4-yl)-acetic acid *(26972-46-3);*

5-oxo-2-thioxo-imidazolidin-4-yl)-acetic acid *(41679-36-1, 61160-00-7);*

3-(2,5-dioxo-imidazolidin-4-yl)-propionic acid *(5624-26-0, 7424-22-8, 17027-50-8);*

(2,5-dioxo-4-phenyl-imidazolidin-4-yl)-acetic acid *(62985-01-7);*

(4-methyl-2,5-dioxo-imidazolidin-4-yl)-acetic acid *(beilstein registry number 145446);*

4-Imidazolidineacetic acid, 4-(hydroxymethyl)-2,5-dioxo-, (4R)- (9CI) *(391870-39-6);*

4-Imidazolidineacetic acid, 4-(4-chlorophenyl)-2,5-dioxo- (9CI) *(250352-11-5);*

4-Imidazolidineacetic acid, α-methyl-2,5-dioxo- (9CI) *(184681-52-5);*

1,3-Diazaspiro[4.4]nonane-6-carboxylic acid, 2,4-dioxo-, cis- (9CI) *(147676-21-9);*

1,3-Diazaspiro[4.5]decane-6-carboxylic acid, 2,4-dioxo- (7CI, 8CI) *(947-10-4);*

1,3-Diazaspiro[4.4]nonane-6-carboxylic acid, 2-oxo-4-thioxo- (9CI) *(197315-95-0);*

4-Imidazolidineacetic acid, 5-oxo-2-thioxo- (9CI) *(41679-36-1);*

1,3-Diazaspiro[4.4]nonane-7-carboxylic acid, 2,4-dioxo- (9CI) *(352656-69-0);*

1,3,7-Triazaspiro[4.4]nonane-8-carboxylic acid, 2,4-dioxo-7-(phenylmethyl)-, (5S,8S)- (9CI) *(265670-86-8);*

Cyclopropanecarboxylic acid, 2-[2,5-dioxo-4-[3-phenyl-2-(phenylmethyl)propyl]-4-imidazolidinyl]-, (1α,2β)-[partial]- (9CI) *(203208-92-8);*

Cyclopropanecarboxylic acid, 2-[4-[2-(3,5-dimethoxyphenyl)ethyl]-2,5-dioxo-4-imidazolidinyl]-, (1α,2β)-[partial]- (9CI) *(203208-94-0);*

Cyclopropanecarboxylic acid, 2-[4-(cyclopentylmethyl)-2,5-dioxo-4-imidazolidinyl]-, (1α,2β)-[partial]- (9CI) *(203208-82-6);*

4,4-Imidazolidinediacetic acid, 2,5-dioxo- (8CI, 9CI) *(5624-17-9);*

4-Imidazolidineacetic acid, 2,5-dioxo-, (R)- (9CI) *(26184-52-1);*

4-Imidazolidineacetic acid, 4-hydroxy-2,5-dioxo- (9CI) *(78703-76-1).*

Transformation C

Transformation C is an alkylation of a protected keto acid, such as 3-oxo-butyric acid tert-butyl ester. Typically the alkylation is performed with no less than two equivalents of a strong base such as sodium hydride, lithium diisopropylamide or lithium hexametyldisilazan in a dry aprotic solvent such as tetrahydrofurane or diethyl ether during cooling conditions (se for example S.N. Huckin and L. Weiler, J. Am. Chem. Soc. 96, 1082, 1974). A typical leaving group is for example a halide or sulfonate.

A numerically huge number of suitably variants (R1, R2 and R3) of ketoacids are commercially available or are described in the scientific literature (for example those shown in List 2 below).

List 2

Examples of suitable intemediate 3 (with CAS registry number in brackets)

2,2-dimethyl-3-oxo-butyric acid methyl ester *(38923-57-8);*

1-acetyl-cyclohexanecarboxylic acid methyl ester *(72335-60-5);*

1-acetyl-cyclopropanecarboxylic acid methyl ester *(38806-09-6);*

6,11-Dodecadienoic acid, 6-methyl-3-oxo-, 1,1-dimethylethyl ester, (6E)- (9CI) *(419567-29-6)*;

Benzenepentanoic acid, 2,3-difluoro-β-oxo-, 1,1-dimethylethyl ester (9CI) *(412950-60-8);*

Benzenepentanoic acid, β-oxo-δ-[(trifluoroacetyl)amino]-, 1,1-dimethylethyl ester (9CI) *(406675-24-9);*

8-Decenoic acid, 5-(methoxymethoxy)-6,9-dimethyl-3-oxo-, 1,1-dimethylethyl ester, (5R,6S)- (9CI) *(405872-43-7);*

Hexanoic acid, 6-chloro-5-hydroxy-3-oxo-, 1,1-dimethylethyl ester, (5R)- (9CI) *(404958-08-3);*

2-Pyrrolidinepentanoic acid, 5-methoxy-β-oxo-1-[(phenylmethoxy)carbonyl]-, 1,1-dimethylethyl ester, (2S)- (9CI) *(382141-43-7);*

2-Benzoxazolebutanoic acid, 5-chloro-β-oxo-, 1,1-dimethylethyl ester (9CI) *(345927-06-2)*;

2-Pyridinepentanoic acid, β-oxo-, 1,1-dimethylethyl ester (9CI) *(334709-97-6);*

Hexanoic acid, 6-cyano-5-hydroxy-3-oxo-, 1,1-dimethylethyl ester, (5S)- (9CI) *(312745-90-7);*

Pentanoic acid, 5-[[(1,1-dimethylethoxy)carbonyl]amino]-3-oxo-, 1,1-dimethylethyl ester (9CI) *(302600-48-2);*

2-Furanpentanoic acid, δ-hydroxy-β-oxo-, 1,1-dimethylethyl ester, (δR)- (9CI) *(214345-59-2);*

Butanoic acid, 4-[(S)-(4-methylphenyl)sulfinyl]-3-oxo-, 1,1-dimethylethyl ester (9CI) *(188709-37-7);*

Butanoic acid, 4-(4-ethenylphenoxy)-3-oxo-, 1,1-dimethylethyl ester (9CI) *(174219-59-1);*

4-Decen-9-ynoic acid, 3-oxo-, 1,1-dimethylethyl ester, (E)- (9CI) *(145130-46-7);*

1-Butanaminium, 4-(1,1-dimethylethoxy)-N,N,N-trimethyl-2,4-dioxo-, chloride (9CI) *(130710-99-5);*

6-Heptenoic acid, 6-fluoro-7-[4-(4-fluorophenyl)-1,2-bis(1-methylethyl)-1H-pyrrol-3-yl]-5-hydroxy-3-oxo-, 1,1-dimethylethyl ester, [S-(Z)]- (9CI) *(128109-14-8);*

Heptanedioic acid, 5-oxo-2-[(3-oxo-1-cyclohexen-1-yl)amino]-, 7-(1,1-dimethylethyl) ester, (S)- (9CI) *(110023-86-4);*

Butanoic acid, 4-[[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)ethyl]thio]-3-oxo-, 1,1-dimethylethyl ester (9CI) *(110651-56-4);*

Cyclohexanebutanoic acid, β-oxo-, 1,1-dimethylethyl ester (9CI) *(106971-01-1);*

3-Azetidinepentanoic acid, 2-methyl-β,4-dioxo-, 1,1-dimethylethyl ester, trans- (9CI) *(104197-08-2).*

Compounds of the invention contain at least one asymmetric carbon atom, and as such exist as optically active isomers. The individual isomers can be prepared from optically pure starting materials such as optically pure 2-amino-2-methyl-succinic acid 4-tert-butyl ester *(147108-45-0)* or derivaties thereof by reacting these with a salt of cyanic acid followed by acidification according to Scheme 3 above. Alternatively individual isomers can be isolated by resolving the racemate by normal techniques such as chromatography.

The compounds of the invention may be evaluated for example in the following assays:

Isolated Enzyme Assays

Matrix Metalloproteinase family including for example MMP12, MMP13.

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 30 minutes at RT in assay buffer (0.1M Tris-HCl, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.040 mM ZnCl and 0.05% (w/v) Brij 35) using the synthetic substrate Mac-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

Recombinant human proMMP13 may be expressed and purified as described by Knauper *et al.* [V. Knauper *et al.*, (1996) The Biochemical Journal 271:1544-1550 (1996)]. The purified enzyme can be used to monitor inhibitors of activity as follows: purified proMMP13 is activated using 1mM amino phenyl mercuric acid (APMA), 20 hours at 21°C; the activated MMP13 (11.25ng per assay) is incubated for 4-5 hours at 35°C in assay buffer (0.1M Tris-HCl, pH 7.5 containing 0.1M NaCl, 20mM CaCl2, 0.02 mM ZnCl and 0.05% (w/v) Brij 35) using the synthetic substrate 7-methoxycoumarin-4-yl)acetyl.Pro.Leu.Gly.Leu.N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl.Ala.Arg.NH_2 in the presence or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 328nm and λem 393nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

A similar protocol can be used for other expressed and purified pro MMPs using substrates and buffers conditions optimal for the particular MMP, for instance as described in C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

Adamalysin family including for example TNF convertase

The ability of the compounds to inhibit proTNFα convertase enzyme may be assessed using a partially purified, isolated enzyme assay, the enzyme being obtained from the membranes of THP-1 as described by K. M. Mohler *et al.*, (1994) Nature 370:218-220. The purified enzyme activity and inhibition thereof is determined by incubating the partially purified enzyme in the presence or absence of test compounds using the substrate 4',5'-Dimethoxy-fluoresceinyl Ser.Pro.Leu.Ala.Gln.Ala.Val.Arg.Ser.Ser.Ser.Arg.Cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 in assay buffer (50mM Tris HCl, pH 7.4 containing 0.1% (w/v) Triton X-100 and 2mM $CaCl_2$), at 26°C for 18 hours. The amount of inhibition is determined as for MMP13 except λex 490nm and λem 530nm were used. The substrate was synthesised as follows. The peptidic part of the substrate was assembled on Fmoc-NH-Rink-MBHA-polystyrene resin either manually or on an automated peptide synthesiser by standard methods involving the use of Fmoc-amino acids and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) as coupling agent with at least a 4- or 5-fold excess of Fmoc-amino acid and HBTU. Ser^1 and Pro^2 were double-coupled. The following side chain protection strategy was employed; Ser^1(But), Gln^5(Trityl), $Arg^{8,12}$(Pmc or Pbf), $Ser^{9,10,11}$(Trityl), Cys^{13}(Trityl). Following assembly, the N-terminal Fmoc-protecting group was removed by treating the Fmoc-peptidyl-resin with in DMF. The amino-peptidyl-resin so obtained was acylated by treatment for 1.5-2hr at 70°C with 1.5-2 equivalents of 4',5'-dimethoxy-fluorescein-4(5)-carboxylic acid [Khanna & Ullman, (1980) Anal Biochem. 108:156-161) which had been preactivated with diisopropylcarbodiimide and 1-hydroxybenzotriazole in DMF]. The dimethoxyfluoresceinyl-peptide was then simultaneously deprotected and cleaved from the resin by treatment with trifluoroacetic acid containing 5% each of water and triethylsilane. The dimethoxyfluoresceinyl-peptide was isolated by evaporation, trituration with diethyl ether and filtration. The isolated peptide was reacted with 4-(N-maleimido)-fluorescein in DMF containing diisopropylethylamine, the product purified by RP-HPLC and finally isolated by freeze-drying from aqueous acetic acid. The product was characterised by MALDI-TOF MS and amino acid analysis.

Natural Substrates

The activity of the compounds of the invention as inhibitors of aggrecan degradation may be assayed using methods for example based on the disclosures of E. C. Arner *et al.*, (1998) Osteoarthritis and Cartilage 6:214-228; (1999) Journal of Biological Chemistry, 274 (10), 6594-6601 and the antibodies described therein. The potency of compounds to act as inhibitors against collagenases can be determined as described by T. Cawston and A. Barrett (1979) Anal. Biochem. 99:340-345.

Inhibition of metalloproteinase activity in cell/tissue based activity

Test as an agent to inhibit membrane sheddases such as TNF convertase

The ability of the compounds of this invention to inhibit the cellular processing of TNFα production may be assessed in THP-1 cells using an ELISA to detect released TNF essentially as described K. M. Mohler *et al.*, (1994) Nature 370:218-220. In a similar fashion the processing or shedding of other membrane molecules such as those described in N. M. Hooper *et al.*, (1997) Biochem. J. 321:265-279 may be tested using appropriate cell lines and with suitable antibodies to detect the shed protein.

Test as an agent to inhibit cell based invasion

The ability of the compound of this invention to inhibit the migration of cells in an invasion assay may be determined as described in A. Albini *et al.*, (1987) Cancer Research 47:3239-3245.

Test as an agent to inhibit whole blood TNF sheddase activity

The ability of the compounds of this invention to inhibit TNFα production is assessed in a human whole blood assay where LPS is used to stimulate the release of TNFα. Heparinized (10Units/ml) human blood obtained from volunteers is diluted 1:5 with medium (RPMI1640 + bicarbonate, penicillin, streptomycin and glutamine) and incubated (160μl) with 20μl of test compound (triplicates), in DMSO or appropriate vehicle, for 30 min at 37°C in a humidified (5%CO_2/95%air) incubator, prior to addition of 20μl LPS (E.

coli. 0111:B4; final concentration 10μg/ml). Each assay includes controls of diluted blood incubated with medium alone (6 wells/plate) or a known TNFα inhibitor as standard. The plates are then incubated for 6 hours at 37°C (humidified incubator), centrifuged (2000rpm for 10 min; 4°C), plasma harvested (50-100μl) and stored in 96 well plates at -70°C before subsequent analysis for TNFα concentration by ELISA.

Test as an agent to inhibit in vitro cartilage degradation

The ability of the compounds of this invention to inhibit the degradation of the aggrecan or collagen components of cartilage can be assessed essentially as described by K. M. Bottomley *et al.*, (1997) Biochem J. 323:483-488.

Pharmacodynamic test

To evaluate the clearance properties and bioavailability of the compounds of this invention an ex vivo pharmacodynamic test is employed which utilises the synthetic substrate assays above or alternatively HPLC or Mass spectrometric analysis. This is a generic test which can be used to estimate the clearance rate of compounds across a range of species. Animals (e,g. rats, marmosets) are dosed iv or po with a soluble formulation of compound (such as 20% w/v DMSO, 60% w/v PEG400) and at subsequent time points (e.g. 5, 15, 30, 60, 120, 240, 480, 720, 1220 mins) the blood samples are taken from an appropriate vessel into 10U heparin. Plasma fractions are obtained following centrifugation and the plasma proteins precipitated with acetonitrile (80% w/v final concentration). After 30 mins at -20°C the plasma proteins are sedimented by centrifugation and the supernatant fraction is evaporated to dryness using a Savant speed vac. The sediment is reconstituted in assay buffer and subsequently analysed for compound content using the synthetic substrate assay. Briefly, a compound concentration-response curve is constructed for the compound undergoing evaluation. Serial dilutions of the reconstituted plasma extracts are assessed for activity and the amount of compound present in the original plasma sample is calculated using the concentration-response curve taking into account the total plasma dilution factor.

In vivo assessment

Test as an anti-TNF agent

The ability of the compounds of this invention as *ex vivo* TNFα inhibitors is assessed in the rat. Briefly, groups of male Wistar Alderley Park (AP) rats (180-210g) are dosed with compound (6 rats) or drug vehicle (10 rats) by the appropriate route e.g. peroral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.). Ninety minutes later rats are sacrificed using a rising concentration of CO_2 and bled out via the posterior vena cavae into 5 Units of sodium heparin/ml blood. Blood samples are immediately placed on ice and centrifuged at 2000 rpm for 10 min at 4°C and the harvested plasmas frozen at -20°C for subsequent assay of their effect on TNFα production by LPS-stimulated human blood. The rat plasma samples are thawed and 175µl of each sample are added to a set format pattern in a 96U well plate. Fifty µl of heparinized human blood is then added to each well, mixed and the plate is incubated for 30 min at 37°C (humidified incubator). LPS (25µl; final concentration 10µg/ml) is added to the wells and incubation continued for a further 5.5 hours. Control wells are incubated with 25µl of medium alone. Plates are then centrifuged for 10 min at 2000 rpm and 200µl of the supernatants are transferred to a 96 well plate and frozen at -20°C for subsequent analysis of TNF concentration by ELISA.

Data analysis by dedicated software calculates for each compound/dose:

$$\text{Percent inhibition of TNF}\alpha = \frac{\text{Mean TNF}\alpha\text{ (Controls)} - \text{Mean TNF}\alpha\text{ (Treated)} \times 100}{\text{Mean TNF}\alpha\text{ (Controls)}}$$

Test as an anti-arthritic agent

Activity of a compound as an anti-arthritic is tested in the collagen-induced arthritis (CIA) as defined by D. E. Trentham *et al.*, (1977) J. Exp. Med. 146.:857. In this model acid soluble native type II collagen causes polyarthritis in rats when administered in Freunds incomplete adjuvant. Similar conditions can be used to induce arthritis in mice and primates.

Test as an anti-cancer agent

Activity of a compound as an anti-cancer agent may be assessed essentially as described in I. J. Fidler (1978) Methods in Cancer Research 15:399-439, using for example the B16 cell line (described in B. Hibner *et al.*, Abstract 283 p75 10th NCI-EORTC Symposium, Amsterdam June 16 – 19 1998).

Test as an anti-emphysema agent

Activity of a compound as an anti-emphysema agent may be assessed essentially as described in Hautamaki *et al* (1997) Science, 277: 2002.

The invention will now be illustrated but not limited by the following Examples:

General procedures

^{1}HNMR and ^{13}CNMR were recorded on a Varian *unity Inova* 400 MHz or a Varian *Mercury*-VX 300 MHz instrument. The central peaks of chloroform-*d* (δ_H 7.27ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or methanol-d_4 (δ_H 3.31 ppm) where used as internal references. Low-resolution mass spectra were obtained on an Agilent 100 LC-MS system equipped with an APCI ionisation chamber. Column chromatography was carried out using silica gel (0.063-0.2 mm) (Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were laboratory grade and used as received.

Abbreviations:

NMP: 1-methyl-2-pyrollidinone

TFA: trifluoroacetic acid

HOBT: 1-hydroxybenzotriazole

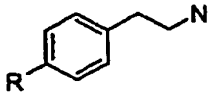
$PdCl_2$ (dppf): bis(diphenylphosphino)ferrocene-palladium(II)chloride dichloromethane complex

THF: tetrahydrofuran

EXAMPLE 1 : 2-(2,5-Dioxo-imidazolidin-4-yl)-acetamides

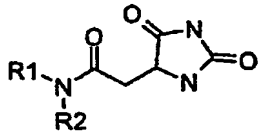
General procedure:

I. Preparation of non-commercial amines



2-(4-Bromo-phenyl)-ethylamine (2mmole, 400mg) was dissolved in 4mL THF (dry, mol sieves) and Di-tert-butyl dicarbonate (1.2eq 2.4mmole 520mg) was added slowly.
The reaction mixture was stirred in room temperature for 1 hour before it was diluted with 100mL ethylacetate and washed with 100mL sat. $NaHCO_3$/aq. The organic phase was dried over Na_2SO_4, filtrated and evaporated to dryness.
The BOC-protected amine was dissolved in a mixture of 10mL toluene, 2.5mL ethanol and 2.5mL 2M Na_2CO_3/aq. $PdCl_2$(dppf) (0.03eq, 50mg) was added together with a corresponding boronic acid (1.05eq, 2.1mmole). The solution was degassed with nitrogen and the vessel was sealed before it was stirred overnight at 80°C.
The reaction mixture was diluted with 50mL toluene and 50mL water. After mixing, the organic layer was transferred directly on to a silica column and purified by chromatography (toluene- ethylacetate).
To remove the protecting group the compound was stirred in a mixture of 5mL conc. HCl in 10mL THF for 30 min. The solution was neutralised with 1M NaOH/aq and extracted with dichloromethane (2x). The combined organic layers was dried over Na_2SO_4, filtrated and evaporated to dryness. The amines were used in the amide synthesis without any further purification.

II. Coupling of amines to 5 hydantoin acetic acid:- amide synthesis

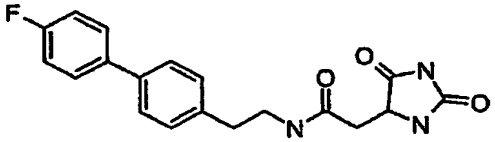


600µL of a 0.15M solution in NMP of 5-hydantoin acetic acid was mixed with 98mg of polystyrene-bound carbodiimide resin (loading 1.28mmol/g). 340µL of a 0.3M solution of HOBT in NMP was added to the mixture and vortexed for 10 minutes before 200µL of a 0.3M solution in NMP of the corresponding amine was added. The reaction mixtures were vortexed overnight at room temperature in sealed vessels.

Resin was removed by filtration and the solution was evaporated to dryness. The products were purified on semiprep-HPLC C_{18}-column (H_2O:CH_3CN, 0.1% TFA buffer, gradient 10% to 95% CH_3CN, 10 min).

The following 2-(2,5-Dioxo-imidazolidin-4-yl)-acetamides were prepared according to the method outlined above:

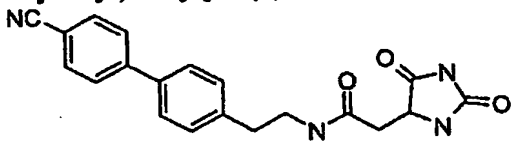
2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4'-fluoro-biphenyl-4-yl)-ethyl]-acetamide



^{1}H NMR (400MHz,DMSO-d_6): 10.56 (1H, s); 8.07 (1H, t); 7.71-.7.65 (2H, m); 7.59-.7.55 (2H, m); 7.32-.7.24 (4H, m); 4.23-4.19 (1H, m); 3.35-3.26 (2H, m); 2.75 (2H , t) 2.56-2.37(2H, m)

APCI-MS m/z: 356.4 [MH^+]

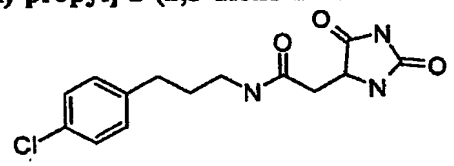
N-[2-(4'-Cyano-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide



^{1}H NMR (400MHz,DMSO-d_6): 10.56 (1H, s); 8.07 (1H, t); 7.92-.7.84 (4H, m); 7.79 (1H, s); 7.69 (2H, d); 7.35 (2H, d); 4.21(1H, t); 3.37-3.27 (2H, m); 2.78 (2H , t) 2.57-2.36(2H, m)

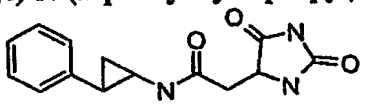
APCI-MS m/z: 363.4 [MH^+]

N-[2-(4-Chloro-phenyl)-propyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide



APCI-MS m/z: 310.34 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-(2-phenyl-cyclopropyl)-acetamide

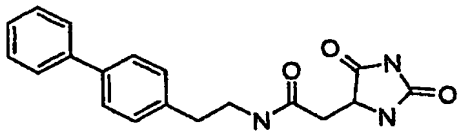


APCI-MS m/z: 274.3 [MH^+]

N-[2-(4-Chloro-phenyl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide

APCI-MS m/z: 296.3 [MH^+]

N-(2-Biphenyl-4-yl-ethyl)-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide



APCI-MS m/z: 338.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(7-methyl-1H-indol-3-yl)-ethyl]-acetamide
APCI-MS m/z: 315.3 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-phenoxy-phenyl)-ethyl]-acetamide
APCI-MS m/z: 354.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-fluoro-phenyl)-ethyl]-acetamide
APCI-MS m/z: 280.3 [MH^+]

N-[2-(4-Bromo-phenyl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 340.3 ; 342.3 [MH^+]

N-[2-(2,4-Dichloro-phenyl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 330.3 ; 332.3[MH^+]

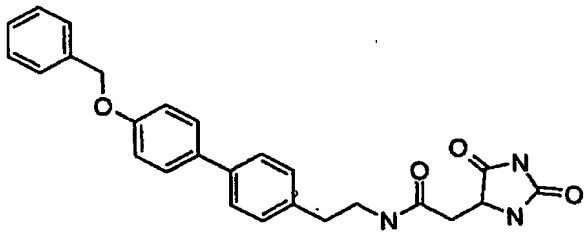
N-[4-(4-Chloro-phenoxy)-benzyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 374.3 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-(4'-methyl-biphenyl-4-ylmethyl)-acetamide
APCI-MS m/z: 338.4 [MH^+]

N-(4'-Chloro-biphenyl-4-ylmethyl)-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 358.4 [MH^+]

N-[2-(3'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 372.4 [MH^+]

N-[2-(4'-Benzyloxy-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide



APCI-MS m/z: 444.5 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-thiophen-3-yl-phenyl)-ethyl]-acetamide

APCI-MS m/z: 344.3 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-thiophen-2-yl-phenyl)-ethyl]-acetamide

APCI-MS m/z: 344.3 [MH^+]

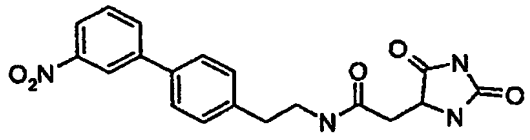
N-[2-(4'-Chloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide

APCI-MS m/z: 372.3 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4'-methylsulfanyl-biphenyl-4-yl)-ethyl]-acetamide

APCI-MS m/z: 384.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(3'-nitro-biphenyl-4-yl)-ethyl]-acetamide



APCI-MS m/z: 383.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4'-methyl-biphenyl-4-yl)-ethyl]-acetamide

APCI-MS m/z: 352.4 [MH^+]

N-[2-(3'-Acetylamino-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 395.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-naphthalen-2-yl-phenyl)-ethyl]-acetamide
APCI-MS m/z: 388.4 [MH^+]

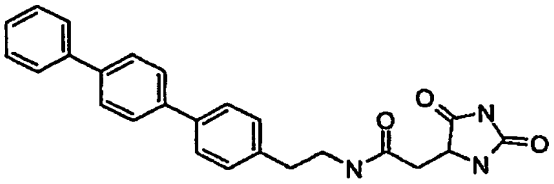
N-[2-(3',5'-Dichloro-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 406.3 ; 408.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(3'-methyl-biphenyl-4-yl)-ethyl]-acetamide
APCI-MS m/z: 352.4 [MH^+]

N-[2-(4-Benzofuran-2-yl-phenyl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 378.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(3'-methoxy-biphenyl-4-yl)-ethyl]-acetamide
APCI-MS m/z: 368.3 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-(2-[1,1';4',1'']terphenyl-4-yl-ethyl)-acetamide



APCI-MS m/z: 414.4 [MH^+]

N-[2-(4'-Acetyl-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide
APCI-MS m/z: 380.4 [MH^+]

N-[2-(4-Benzo[b]thiophen-2-yl-phenyl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide

APCI-MS m/z: 394.4 [MH^+]

N-[2-(4'-Cyanomethyl-biphenyl-4-yl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide

APCI-MS m/z: 377.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-pyridin-3-yl-phenyl)-ethyl]-acetamide

APCI-MS m/z: 339.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-{2-[4-(1H-pyrrol-2-yl)-phenyl]-ethyl}-acetamide

APCI-MS m/z: 327.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-furan-3-yl-phenyl)-ethyl]-acetamide

APCI-MS m/z: 328.4 [MH^+]

2-(2,5-Dioxo-imidazolidin-4-yl)-N-[2-(4-furan-2-yl-phenyl)-ethyl]-acetamide

APCI-MS m/z: 328.4 [MH^+]

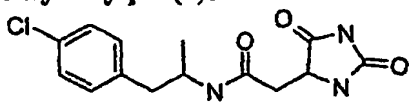
2-(2,5-Dioxo-imidazolidin-4-yl)-N-(2-thiophen-2-yl-ethyl)-acetamide

APCI-MS m/z: 268.3 [MH^+]

N-[2-(4-tert-Butyl-phenyl)-ethyl]-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide

APCI-MS m/z: 318.4 [MH^+]

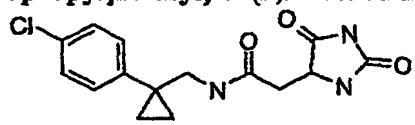
N-[2-(4-chlorophenyl)-1-methylethyl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide



^{1}H NMR (400MHz,DMSO-d_6): 10.55(1H, d); 7.88 (1H, dd); 7.76 (1H, d); 7.33-7.31 (2H, m); 7.21-7.19 (2H, m); 4.19-4.16 (1H, m); 3.94-3.88 (1H, m); 2.77-2.32 (4H, m); 0.99 (3H, dd)

APCI-MS m/z: 310.3 [MH^+]

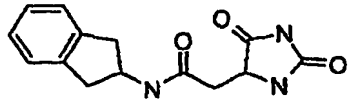
N-{[1-(4-chlorophenyl)cyclopropyl]methyl}-2-(2,5-dioxoimidazolidin-4-yl)acetamide



^{1}H NMR (400MHz,DMSO-d_6): 10.53(1H, d); 7.95 (1H, t); 7.73 (1H, s); 7.33-7.25 (4H, m); 4.18-4.15 (1H, m); 3.39-3.22 (2H, m); 2.54-2.37 (2H, m); 0.90-0.88 (2H, m); 0.76-0.73 (2H, m)

APCI-MS m/z: 322.3 [MH^+]

N-2,3-dihydro-1H-inden-2-yl-2-(2,5-dioxoimidazolidin-4-yl)acetamide

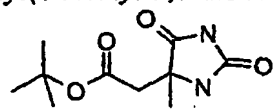


^{1}H NMR (400MHz,DMSO-d_6): 10.54(1H, d); 8.24 (1H, d); 7.82 (1H, s); 7.22-7.20(2H, m); 7.16-7.13 (2H , m); 4.47-4.42 (1H, m); 4.22-4.19(1H, m); 3.19-3.12(2H, m); 2.80-2.72 (2H, m); 2.54-2.36 (2H, m)

APCI-MS m/z: 274.2 [MH^+]

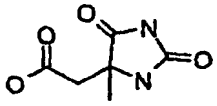
EXAMPLE 2: (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetamides

I. tert-butyl(4-methyl-2,5-dioxoimidazolidin-4-yl)acetate.



Tert-butyl acetoacetate (200mg; 1.3mmol), KCN (165mg; 2.5mmol) and $(NH_4)_2CO_3$ (605mg; 6.3mmol) was suspended in EtOH (2mL) and H_2O (2mL) in a sealed tube. The mixture was heated to 85-90 °C and a solution was obtained, the heating was continued over night. The resulting slightly yellow solution was allowed to cool to roomtemperature and a precipitate was formed. The mixture was neutralised with 5%$NaHSO_4$ (aq) and diluted with H_2O (30mL). The slurry was extracted with EtOAc (2x50 mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to give the title compound as a colourless solid. Obtained 210 mg (73% yield).
^{1}H-NMR(DMSO-D6): δ 10.58 (1H, s), 7.91 (1H, s), 2.76+2.39 (1H each, ABq), 1.35 (9H, s), 1.23 (3H, s) ppm.

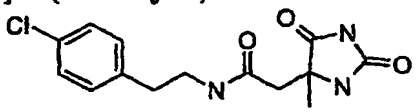
II. (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetic acid



Deprotection (Greene, T.W: Protective groups in organic synthesis, pp 245-247, Wiley 1991) afforded the title compound.

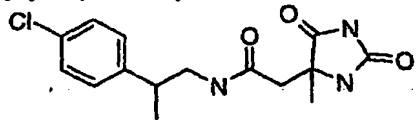
The following (4-methyl-2,5-dioxoimidazolidin-4-yl)acetamides were prepared by coupling of the appropiate amine to (4-methyl-2,5-dioxoimidazolidin-4-yl)-acetic acid by the method described in Example 1.

N-[2-(4-chlorophenyl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide



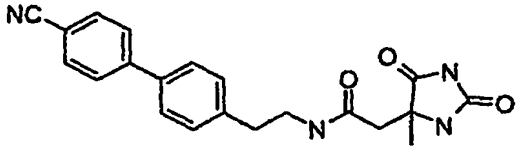
^{1}H NMR (400MHz,DMSO-d_6): 10.42(1H, s); 7.94(1H, t); 7.35(1H, s); 7.35-7.31 (2H, m); 7.24-7.21 (2H, m) ; 3.21 (2H, q); 2,67 (2H, dd); 2.53-2.36 (2H, m); 1.21 (3H, s)
APCI-MS m/z: 310.3 [MH$^+$]

N-[2-(4-chlorophenyl)propyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide



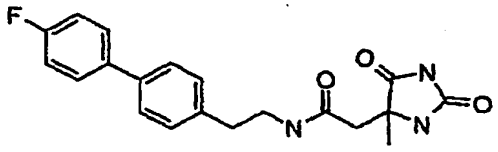
^{1}H NMR (400MHz,DMSO-d_6): 10.42 (1H,m); 7.89-7.86 (1H, m); 7.65-7.64 (1H, m); 7.35-7.32 (2H, m); 7.24-7.22 (2H, m); 3.19-3.09 (2H, m); 2.87-2.77 (1H, m); 2.53-2.37 (2H, m); 1.19 (3H, d); 1.14 (3H, d)
APCI-MS m/z: 324.4 [MH$^+$]

N-[2-(4'-cyano-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide



APCI-MS m/z: 377.3 [MH$^+$]

N-[2-(4'-fluoro-1,1'-biphenyl-4-yl)ethyl]-2-(4-methyl-2,5-dioxoimidazolidin-4-yl)acetamide



^{1}H NMR (400MHz,DMSO-d_6): 10.42 (1H,s); 7.99 (1H, t); 7.97-7.65 (3H, m); 7.56 (2H, d); 7.30-7.24 (4H, m); 3.28-3.23 (2H, m); 2.73-2.70 (2H, m); 2.54-2.39 (2H, m); 1.22 (3H, s)

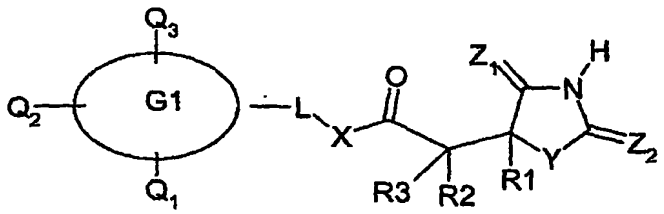
APCI-MS m/z: 370.4 [MH^+]

Ink. t. Patent- och reg.verket
2002 -08- 27

CLAIMS

What we claim is:

1. A compound of the formula 1 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof



Formula 1

wherein

X is selected from NR4, O, CH2;

Y is selected from NH, N-methyl;

Z1 is selected from O, S, and **Z2** is selected from O, S, such that at least one of **Z1** and **Z2** is O;

R1 is selected from H, hydroxy, alkoxy, haloalkoxy, alkyl, heteroalkyl, heterocycloalkyl, aryl, heteroaryl, heterocycloalkylalkyl, alkylaryl, alkylheteroaryl, alkyl heterocycloalkyl, heteroalkylaryl, heteroalkylheteroaryl,arylalkyl, arylheteroalkyl,heteroarylalkyl, heteroarylheteroalkyl,arylaryl, arylheteroaryl,heteroarylaryl,heteroarylheteroaryl;

R1 is optionally substituted by one or more substituents selected from (C1-3)alkyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, thiol, alkylthiol, arylthiol, alkylsulfon, arylsulfon, aminosulfon, alkylaminosulfon, alkylaminosulfon, arylaminosulfon,primary, secondary or tertiary amino, amido, alkylamido, dialkylamido, cyano, sulfonamino, alkylsulfonamino, arylsulfonamino, amidino, N-aminosulfon-amidino, guanidino, N-cyano-guanidino, thioguanidino, 2-nitro-ethene-1,1-diamin, carboxylat, alkyl-carboxylat;

R2 is selected from H, (C1-3)alkyl;

R3 is selected from H, (C1-3)alkyl;

optionally **R1** and **R2** together with the carbon atoms to which they are attached may form a 5- or 6-membered saturated cycloalkyl or heterocyloalkyl ring;

ptionally **R2** and **R3** together with the carbon atom to which they are attached may form a 5- or 6-membered saturated cycloalkyl or heterocyloalkyl ring;

R4 is selected from H, methyl, ethyl, isopropyl;

L is (C1-6)alkyl, (C1-6)alkynyl, or **L** is (C1-C5)heteroalkyl wherein the heteroalkyl contains a heteroatom or group selected from O, N, S, SO, SO2, CO, or **L** is selected from (C3-6)cycloalkyl, (C3-6)heterocycloalkyl;

L is optionally substituted with one or more substituents selected from (C1-4)alkyl, halogen, halo-(C1-4)alkyl, halo-(C1-4)alkoxy, (C1-4)alkoxy, wherein optionally a substituent may be attached to L at two points to form a ring or optionally a substituent may be attached to both L and G1 to form a ring;

G1 is a monocyclic, bicyclic or tricyclic group comprising one, two or three ring structures each of 3 to 7 ring atoms selected from cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, wherein at least one ring structure is aryl or heteroaryl;

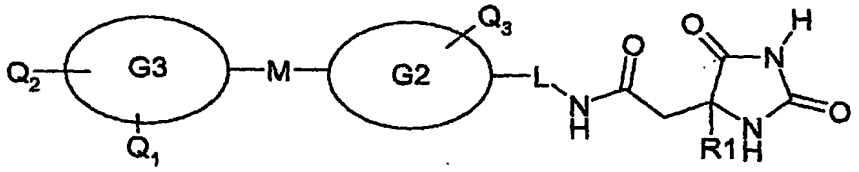
when **G1** is a bicyclic or tricyclic group each ring structure is joined to the next ring structure by a direct bond, by –O-, –S-, –NH-, –CO-, –CH2O-, -OCH2-, –CH2S-, -SCH2-, -C≡C-, -SO2-, -CH2, -NCO- or is fused to the next ring structure;

Q1, **Q2** and **Q3** are each independently selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

any alkyl radical within any of **Q1**, **Q2**, and **Q3** may itself be optionally substituted by one or more substituents selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl; methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

provided that the compound of Formula 1 is not *N*-{2-[3-(1*H*-Benzoimidazol-2-ylsulfanylmethyl)-2-methyl-phenylsulfanyl]-ethyl}-2-(2,5-dioxo-imidazolidin-4-yl)-acetamide.

2. A compound of the formula 2 or a pharmaceutically acceptable salt or an <u>in vivo</u> hydrolysable ester thereof



<u>Formula 2</u>

wherein

R1 is selected from H, (C1-6)alkyl, -(C1-6)alkylphenyl, -(C1-6)heteroalkyl, -(C1-6)alkyl-carboxylic acid, heterocycloalkyl, -(C1-6)alkyl-heterocycloalkyl, heteroaryl or -(C1-6)alkyl-heteroaryl; preferred heteroaryls are pyridine, diazines (such as pyrimidine) or azoles (such as imidazol), preferred heterocycloalkyls are morpholino, piperidine or piperazine; preferred heteroalkyls are amino-(C1-6)alkyl-; preferred substituents on

heteroaryl are halogen, preferred substituents on amines in heteroalkyls and heterocycloalkyls are H, alkyl, alkylsulfon, alkylaminocarbonyl or alkyloxycarbonyl;

L is (C1-6)alkyl, (C1-6)alkynyl or L is (C1-5)heteroalkyl wherein the heteroalkyl contains a heteroatom or group selected from O, S, or L is (C3-6)cycloalkyl;

L is optionally substituted with one or more substituents selected from (C1-4)alkyl, halogen, halo-(C1-4)alkyl, halo-(C1-4)alkoxy, (C1-4)alkoxy, wherein optionally a substituent may be attached to L at two points to form a ring;

G2 is a 5- or 6-membered aryl or heteroaryl ring;

M is selected from a direct bond, -O-, -S-, -C≡C-, -CH2O-, -OCH2-;

G3 is a monocyclic or bicyclic group comprising one or two ring structures each of 3 to 7 ring atoms selected from cycloalkyl, aryl, heterocycloalkyl, or heteroaryl, wherein when G3 is bicyclic at least one cyclic group is aryl or heteroaryl;

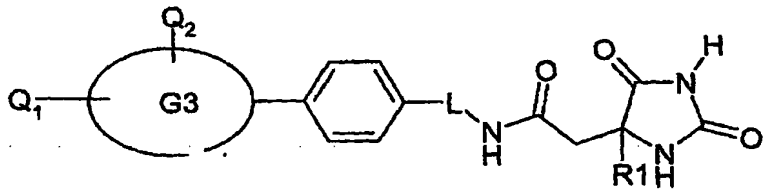
when G3 is a bicyclic group each ring structure is joined to the next ring structure by a direct bond, –O-, –S-, –NH-, –CO-, –CH2O-, –CH2S-, -C≡C-, -SO2-, -CH2, -NCO- or is fused to the next ring structure;

Q1, Q2 and Q3 are each independently selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

any alkyl radical within any of Q1, Q2, and Q3 may itself be optionally substituted by one or more substituents selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl,

N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl.

3. A compound of the formula 2 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof

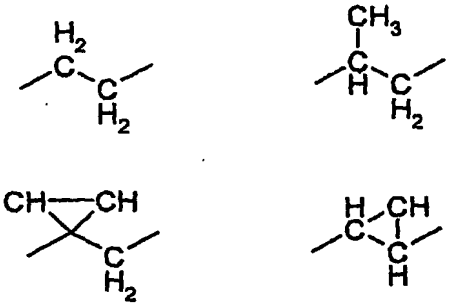


Formula 3

wherein

R1 is selected from H, (C1-6)alkyl, -(C1-6)alkylphenyl, -(C1-6)heteroalkyl, -(C1-6)alkyl-carboxylic acid, heterocycloalkyl, -(C1-6)alkyl-heterocycloalkyl, heteroaryl or -(C1-6)alkyl-heteroaryl;

L is selected from:



G3 is a monocyclic group or **G3** is a fused bicyclic group comprising two ring structures each of 3 to 7 ring atoms selected from aryl or heteroaryl;

Q1 and Q2 are each independently selected from hydrogen, fluorine, chlorine, bromine, iodine, hydroxy, thiolo, nitro, nitroso, cyano, amino, methyl, vinyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, tert-butyl, trifluoromethyl, pentafluoroethyl, hydroxymethyl, formyl, N-methylformamide, methylformate, ethylformate, acetyl, methoxymetyl, cyanomethyl, trifluoromethoxy,methoxy, ethoxy, isopropoxy, butoxy, tertbutoxy, acetoxy, methylsulfide, ethylsulfide, propylsulfide, trifluoromethylsulfide, methylsulfonyl, trifluoromethylsulfonyl, aminosulfonyl, ethylsulfonyl, methylsulfoxyl, cyanoamin, hydrazine, methylamine, ethylamine, propylamine, butylamine, dimethylamine, diethylamine, formylamine,acetylamine, aminocarbonylamine, methylsulfonamine, ethyloxycarbonylamine,methylsulfonyl;

or Q1 is a group W-U-V-

wherein

V is attached to G3 and V is selected from CH2, O, S, SO, SO2, N, NCO, CON, OCON, NCON, NSO2, SO2N or CO;

U is (C1-C5)alkyl;

W is selected from hydroxy, amino, (C1-3)alkylamino, (C1-3)alkylamido, (C1-3)alkylcarbamate, (C1-3)alkylurea, cyano or (C1-3)alkyl sulfonyl;

optionally W may be attached to G3 so that together W, U, V and G3 from a ring.

4. A pharmaceutical composition which comprises a compound of the formula 1 as claimed in claim 1 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

5. A pharmaceutical composition which comprises a compound of the formula 2 as claimed in claim 2 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition which comprises a compound of the formula 3 as claimed in claim 3 or a pharmaceutically acceptable salt or an in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

7. A method of treating a metalloproteinase mediated disease or condition which comprises administering to a warm-blooded animal a therapeutically effective amount of a compound of the formula 1 or formula 2 or formula 3 or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof.

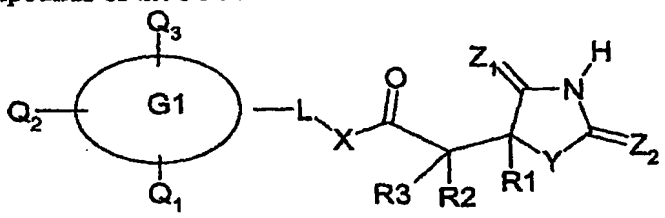
8. Use of a compound of the formula 1 or formula 2 or formula 3 or a pharmaceutically acceptable salt or in vivo hydrolysable precursor thereof in the preparation of a medicament for use in the treatment of a disease or condition mediated by one or more metalloproteinase enzymes.

Ink. t. Patent- och reg.verket
2002 -08- 2 7

A B S T R A C T

COMPOUNDS

Compounds of the Formula 1



useful as metalloproteinase inhibitors, especially as inhibitors of MMP12.